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(54) Drug delivery arrangement.

(57) An arrangement for delivering a drug aerosol comprises a sensor (3) which detects turbulent air flow during inhalation and causes the nebulizer (8,9,10,11,12,13) to generate the aerosol only during the inhalation phase of the breathing cycle. Airflow is diverted from the sensor during exhalation.

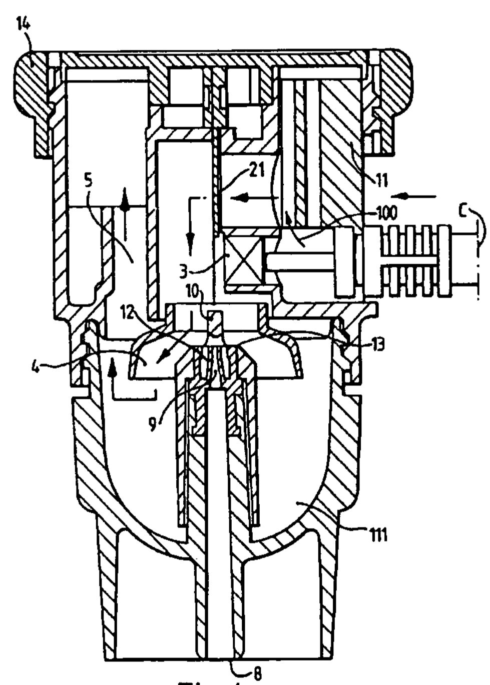

Fig.4.

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The present invention relates to a delivery arrangement for delivering a drug aerosol to the respiratory system of a patient.

It is desirable for such a drug delivery arrangement to generate a drug aerosol selectively during inhalation, so that the drug is not wasted during exhalation. It has previously been proposed to make a drug delivery device in which the aerosol of the drug is formed periodically at the same rate as the normal breathing rate, but such a device requires the patient to coordinate his breathing with the periodic drug delivery. However, in many cases patients are not able to coordinate their breathing in this way. Furthermore, other proposed devices for delivering drug to the respiratory system require an increased respiratory flow which, in practice, cannot always be achieved, e.g. by children, especially during an asthma attack.

An object of the present invention is to overcome or alleviate the above problems.

Accordingly the invention provides a drug delivery arrangement for delivering a drug aerosol to the respiratory system of a patient, comprising nebulizer means arranged to generate a drug aerosol in the air stream inhaled by the patient, sensor means responsive to the air flow due to the breathing of the patient, and control means responsive to a control signal generated by said sensor means to cause said nebulizer means to generate said aerosol selectively during the inhalation phase of the patient's breathing cycle.

Preferably the sensor means is responsive to turbulence in said air flow and may comprise a microphone, for example.

Preferred embodiments of the invention are described below by way of example with reference to Figures 1 to 6 of the accompanying drawings wherein:

Figure 1 is a cross-section showing a mouth piece having a sensor mounted therein for use in one embodiment of the invention;

Figure 2 is an axial cross-section of a valved delivery system for use in an alternative embodiment of the invention;

Figure 3 is a plan view of the delivery system shown in Figure 2 (with the top cap removed);

Figure 4 is an axial cross-section taken at right angles to the cross-section of Figure 2;

Figure 5 is a schematic representation of a further embodiment utilizing a remotely located sensor;

Figure 6 is a block diagram of a control circuit for controlling the valved delivery system of Figures 2 to 4 or Fig. 5, and Figure 7 is a timing diagram.

Figure 1 shows a mouthpiece for use in one embodiment of the invention which comprises a microphone 3located in a chamber 4 which has an aperture 2 communicating with the airflow through the mouthpiece and directed approximately parallel to the access of the air flow. Consequently, turbulence is generated around the aperture 2 during inhalation (i.e. the air flows from left to right in Figure 1) whereas little, if any, turbulence is generated during exhalation (when the air flow is in the direction from right to left in Figure 1). An output from the microphone is connected to a control circuit (such as that described below with reference to Figure 6) which controls the operation of a nebulizer (not shown) which can be inserted into a port 1 in the mouthpiece. The nebulizer may be of the type shown in GB 838453 and GB 1283988.

The nebulizer is arranged to generate an aerosol of finely divided drug particles (0.5 to 5 micro meters for bronchial deposition and 0.5 to 2 micro meters for alveolar deposition) during each inhalation phase of the breathing cycle. The nebulizer may be arranged to generate a predetermined amount of aerosol for a predetermined number of breathing cycles, thereby enabling a predetermined amount of drug to be delivered.

Figures 2, 3 and 4 shows an alternative valved delivery system in which the air flow is directed over a microphone 3 (Figure 4) via a flap valve 21 only during inhalation and is directed in a different path during exhalation. The patient inhales and exhales through a mouthpiece port A (Figure 2) and air is inhaled into the device via port C and exhaled from the device via port (B).

When the patient breaths in air it is drawn through port C, as indicated by arrow 100 (Figure 4) and passes via a silencer baffle 11 to an inlet valve 21. The silencer baffle prevents nebulizer noise escaping and also isolates the microphone 3 from external noise. The silencer baffle can be replaced by a sealed filter where absolute system to atmosphere containment is required.

As the air passes through inlet valve 21 the resulting turbulence is detected by the microphone 3 and the air then passes through a liquid drug nebulizer baffle 4 and up via port 5 to the patient at port A (Figure 2). When the patient breaths out the air passes via gallery 6 (Figures 2 and 3) to an exhalation valve 7 which is shown as a flexible flap valve. The air then exits via port B to the atmosphere. The gallery 6 prevents any liquid in the airstream of the patient from returning to the nebulizer reservoir; instead any such liquid passes out through the exhalation valve 7. An exhalation filter can be connected to port B if required.

When the microphone detects the turbulence during the inhalation phase of the breathing cycle, the nebulizer is supplied with compressed air via an inlet connector 8 (Figure 4) under the control of a solenoid valve (Figure 5). The schematic representation of Figure 5 of the overall system (described more fully later), shows the sensor remotely located, however the system is equally applicable to a sensor mounted in the mouthpiece (see Figure 1) or in a valved system (see Figures 2, 3 and 4). The compressed air passes

through a jet 9 at high velocity and strikes a bar 10 which divides the air flow into two high velocity horizontal streams. These two high velocity horizontal streams generate a low pressure area above a reservoir 111 which draws liquid into liquid jets 12. The liquid from these jets is spread out into a thin film and formed into small particles at edge 13. Particles larger than a predetermined size (e.g. 5 micro meters) impact on a baffle 4 whereas smaller particles of the desired size are drawn down and out of the nebulizer by air flow through the baffle. This nebulizer design is shown in more detail in the above-mentioned GB 838453 and GB 1283988 which are.incorporated herein by reference.

The microphone 3 is an ultra miniature electret condenser microphone (having a frequency response of 50 Hz to 84 Khz) and is desirably mounted close to the valve flap 21.

The delivery system is fully reusable, and in particular it will be noted that it includes a screwed cap 14 which can be unscrewed and removed to gain access to the inlet valve 21 and exhalation valve 7. These can be removed, together with the microphone 3 which is locked in position. Once the microphone is removed all the other components can be cleaned in hot water (> 65°C) or autoclaved.

Figure 5 shows an alternative embodiment comprising a mouthpiece 101, a valved delivery system and nebulizer arrangement 102 (which is similar but not identical to that shown in Figures 2 to 4) and a filter 103 which is connected to an exhalation port of the valved delivery system 102. The delivery system 102 differs from that shown in Figures 2 to 4 in that the microphone is mounted remotely in a sensor unit 30 and is connected to the delivery system 102 by a flexible tube 105. The mouth of the tube is located near a valve flap (not shown) in an inlet of the valved delivery system (102) and noise generated at this inlet is transferred along the tube to the microphone in the sensor unit 30. An airline 104 supplies compressed air to the nebulizer and is controlled by a solenoid valve 60 under the control of a control unit 40. The unit also includes a compressor 50 to supply the compressed air.

An electronic control system which can be used to control the above-described arrangement will now be described with reference to Figure 6.

Figure 6 shows a microphone 3 connected directly to one input of a comparator 203 and indirectly via an amplifier 201 and a smoothing circuit 202 to the other input of the comparator. Accordingly the comparator 203 generates an output signal only when a sudden fluctuation in the output of microphone 3 occurs (due to turbulence at the beginning of inhalation) and does not generate a signal when the microphone detects only normal ambient noise due to the air compressor 50 (Figure 5) for example. The output of comparator 203 feeds a monostable multivibrator 204 which has a non-retriggerable period of three seconds and accordingly generates a higher output for three seconds, thereby triggering a monostable multivibrator 205 for a period of one second and opening the solenoid valve 60 for one second. Each of these multi vibrators is triggered by the positive edge of the input wave form and they may be constituted by a type 4538 dual multi vibrator for example.

In order to prevent the multi vibrators 204 and 205 from being energised by a momentary signal due to a sudden ambient noise, for example a gating circuit is provided, comprising a NAND gate 209 having one input coupled via a single retriggerable monostable multivibrator 208 to the output of comparator 203 and having its other input coupled to a similar retriggerable monostable multivibrator 207 whose input is in turn, connected to the output of a further monostable multivibrator 206, whose input is also connected to the output of comparator 203. The output of gate 209 is connected to reset terminals of monostable multivibrators 204 and 205.

Monostable multivibrators 206 and 207 form a delay mono stable arrangement. Monostable 206 is triggered by comparator 203 producing a 20ms positive going pulse. The negative edge of this pulse triggers monostable 207 which produces a positive going 2ms pulse. A 2ms pulse is therefore, generated 20ms after the trigger from comparator 203 is received. If, during this 20 millisecond period the continuous series of pulses from the output of comparator 203 has ceased (indicating that merely ambient noise and not turbulence was detected) then the output of monostable multivibrator 208 will be HIGH NAND gate 209 will generate an output signal which will reset the monostable multivibrators 204 and 205 and inhibit the operation of the nebulizer. The performance of the circuit will be understood by reference to the timing diagram Fig. 7.

Referring to Figure 7 in which the left hand side L represents the true trigger timing sequence whereas the right hand side R represents a false trigger timing sequence.

On left hand side L:- line 700 represent the output of the comparator 203 having a sequence spacing of less than 2ms;

line 701 represents the sequence of the monostable 206 having a 20ms vibration period;

line 702 represents the sequence of the monostable 207 producing a 2ms pulse which is generated 20ms after the trigger from the comparator 203 is received.

lines 203/704 represent the timing relationship between the monostable 208 and the NAND gate 209 which generate an output signal which will reset the monostable vibrators 204 and 205 after 3 seconds and 1 second respectively as shown at lines 705 and 706.

A sequence of false trigger timing is shown at R in figure 7 in which corresponding lines for the false

trigger are allocated the same line numbers as under L but qualified by A.

The sequence is relative to a 20ms vibration period of the monostable 206 which is reflected in the same vibration period for monostable 204 and 205 with a negative 10ms pulse of monostable 208 as well as positive and negative 2ms pulse for monostable 207 and 209 coincident with the end of the 20ms vibration period of the monostable 206.

The arrangement is set to give a predetermined number of doses of drug aerosol, one during each inhalation phase of the breathing cycle of the patient, each dose cycle taking a minimum of three seconds, corresponding to 20 breaths per minute. This allows for stable operation, with a nominal nebulizer operation period of one second and a nominal two second pause to recharge the nebulizer driving system.

Claims

1. A drug delivery arrangement for delivering a drug aerosol to the respiratory system of a patient, comprising nebulizer means arranged to generate a drug aerosol in the airstream inhaled by the patient, sensor means responsive to turbulence in the airflow due to the breathing of the patient, and control means responsive to a control signal generated by said sensor means to cause said nebulizer means to generate said aerosol selectively during the inhalation phase of the patient's breathing cycle.

2. A drug delivery arrangement according to claim 1 which comprises a directional valve which is located in the path of and operated by said airflow and arranged to direct the airflow to said sensor means during a predetermined phase of the breathing cycle.

3. A drug delivery arrangement according to claim 1 wherein said sensor means is exposed to forward and reverse airflow during the inhalation and exhalation phases of the breathing cycle and is so disposed that it responds selectively to either the forward or reverse airflow.

4. A drug delivery arrangement according to claim 3 wherein said sensor means is located in a chamber having an aperture which is exposed to said air flow and is directed transverse to a plane which is normal to the axis of said airflow.

5. A drug delivery arrangement according to claim 1 wherein said sensor means comprises a microphone.

6. A drug delivery arrangement according to claim 5 wherein said control means is arranged to smooth the output of said microphone, to compare the instantaneous output of the microphone with the smoothed output of the microphone and to generate said control signal in response to the comparison of said outputs.

7. A drug delivery arrangement according to claim 1 or claim 7 wherein said control means is responsive to changed in the amplitude form of the microphone so as to mitigate the effects of continuous background noise.

8. A drug delivery arrangement according to claim 1 wherein said control means includes gating means which is arranged to inhibit the generation of said control signal unless said sensor means generates an output signal for longer than a predetermined period.

9. A drug delivery arrangement according to claim 8 wherein said gating means includes a non-retriggerable monostable multivibrator and a retriggerable monostable multivibrator connected to a common input and having their outputs connected to respective inputs of a logic gate.

10. A drug delivery arrangement according to claim 1, wherein said sensor means is pressure-sensitive and is coupled by a flexible tube to a further tube through which the patient breaths.

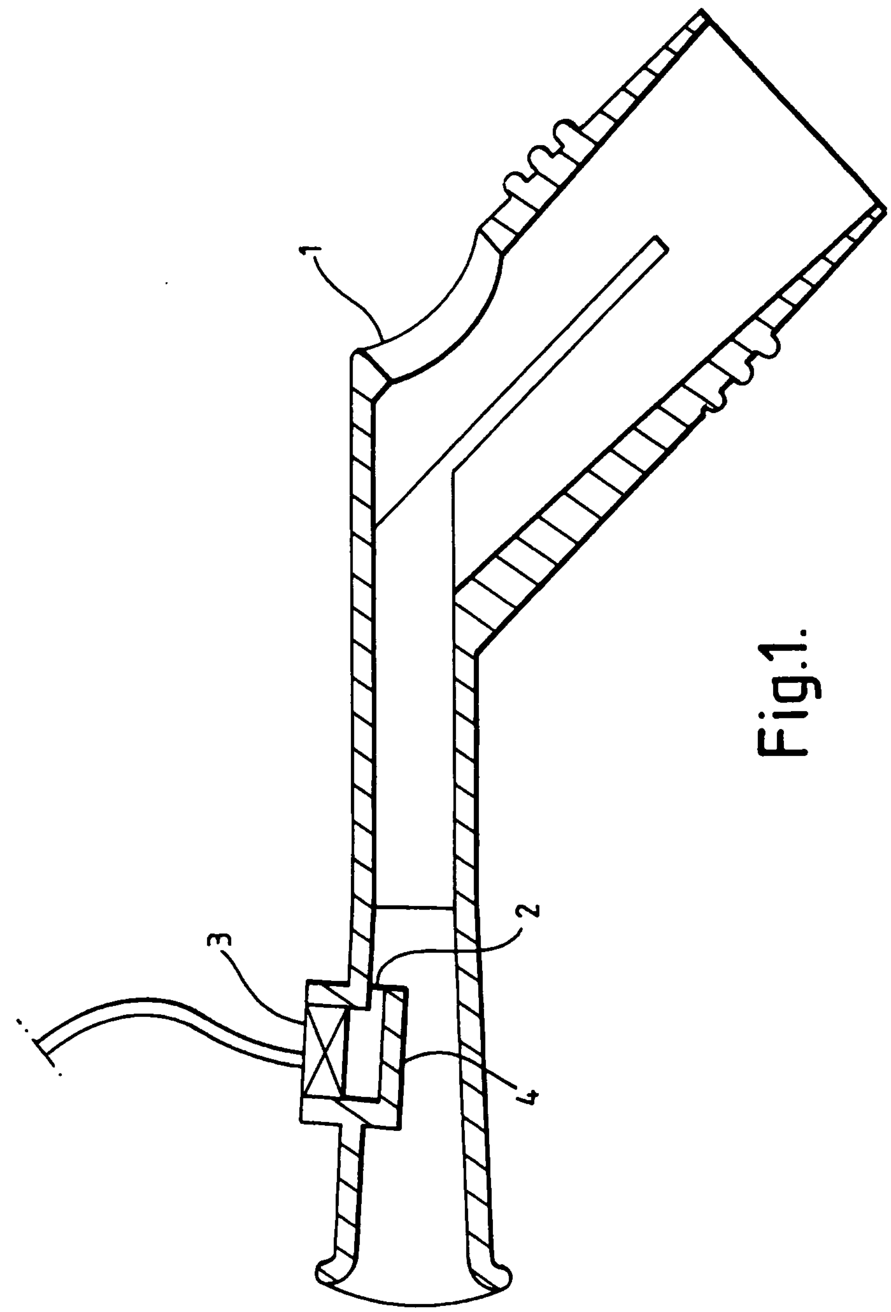

Fig.1.

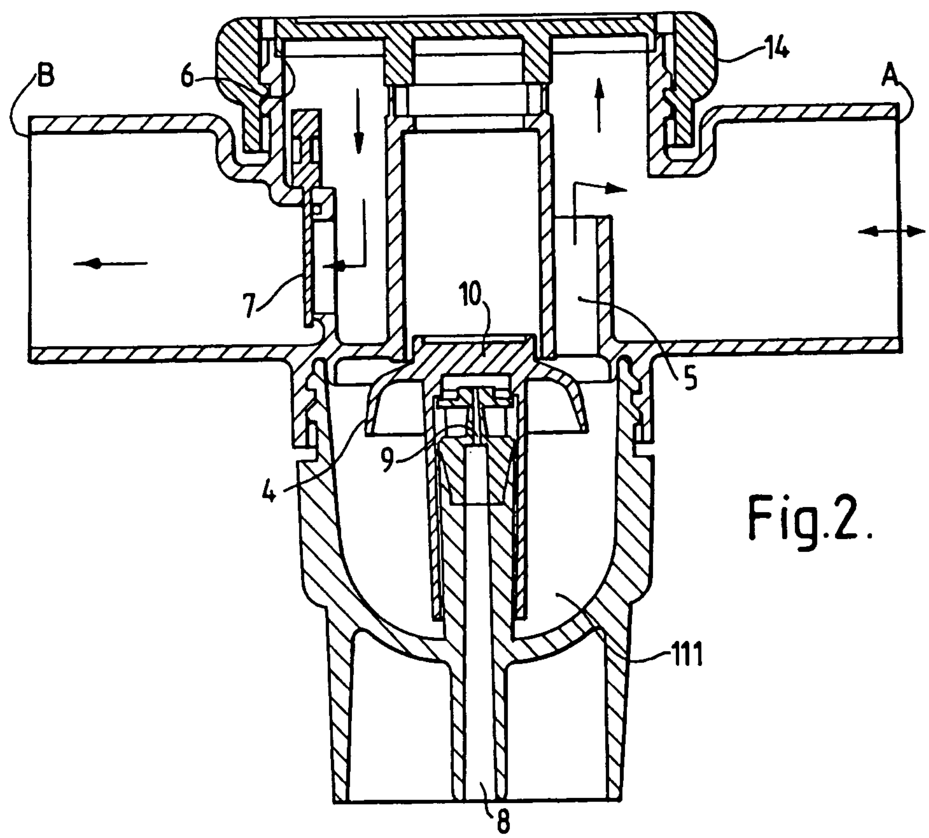

Fig.2.

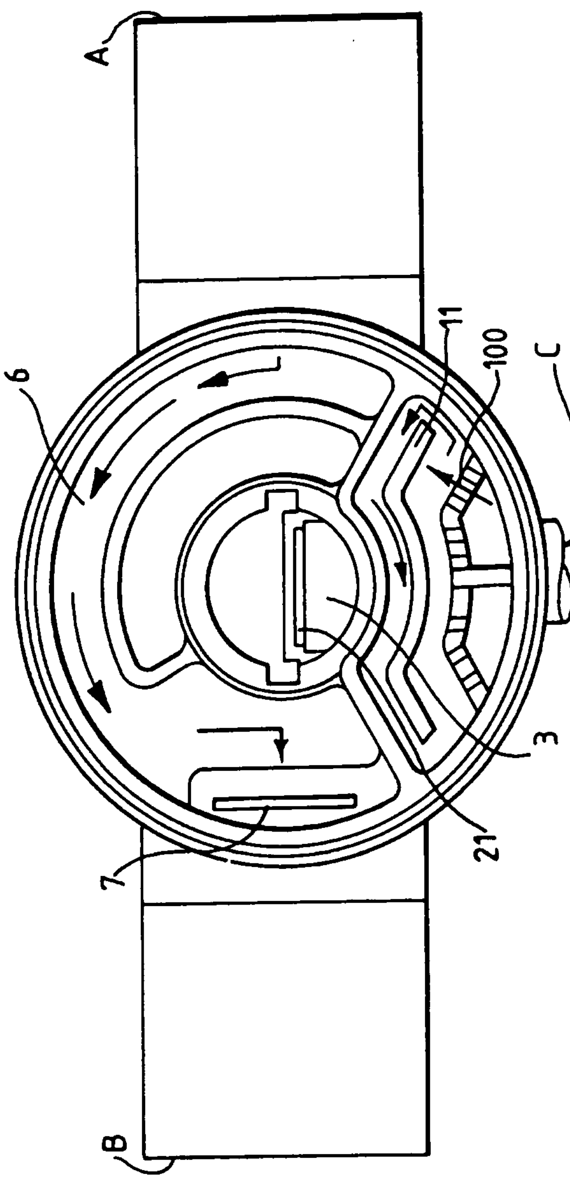

Fig.3.

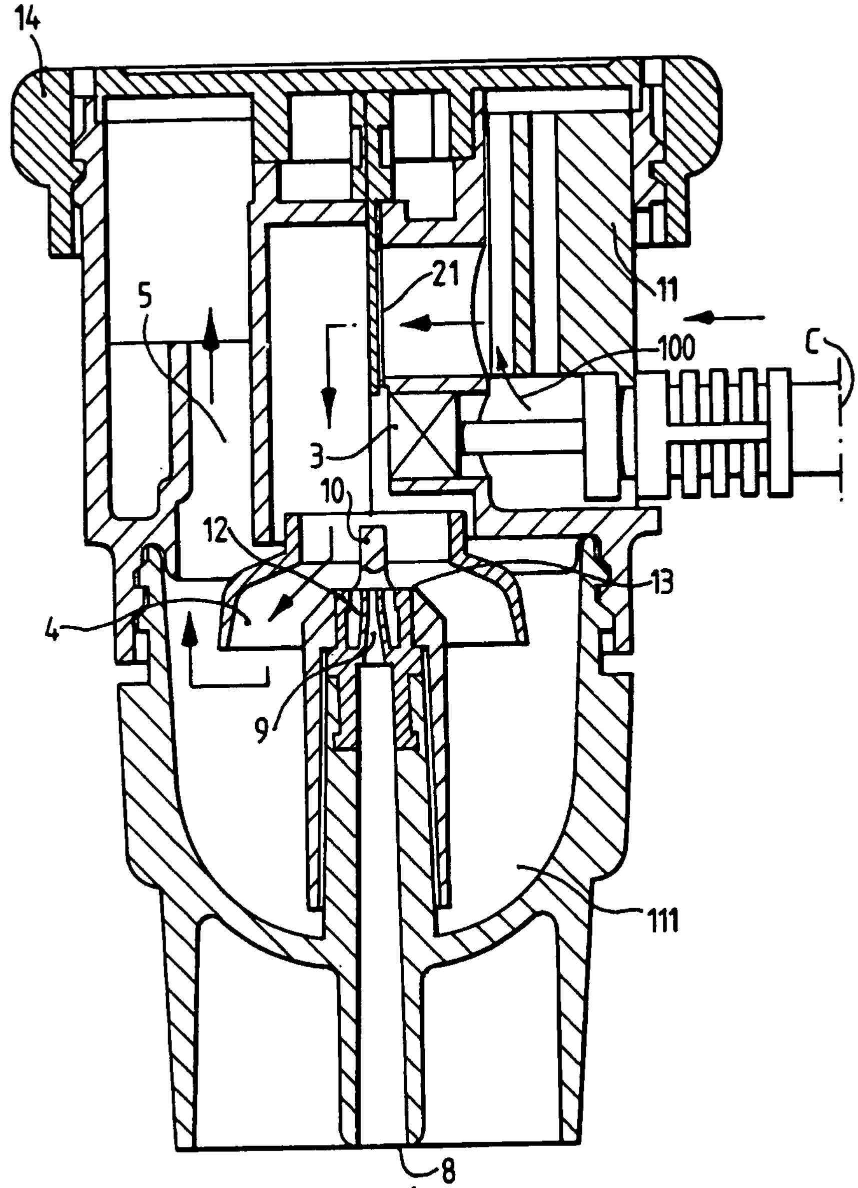

Fig.4.

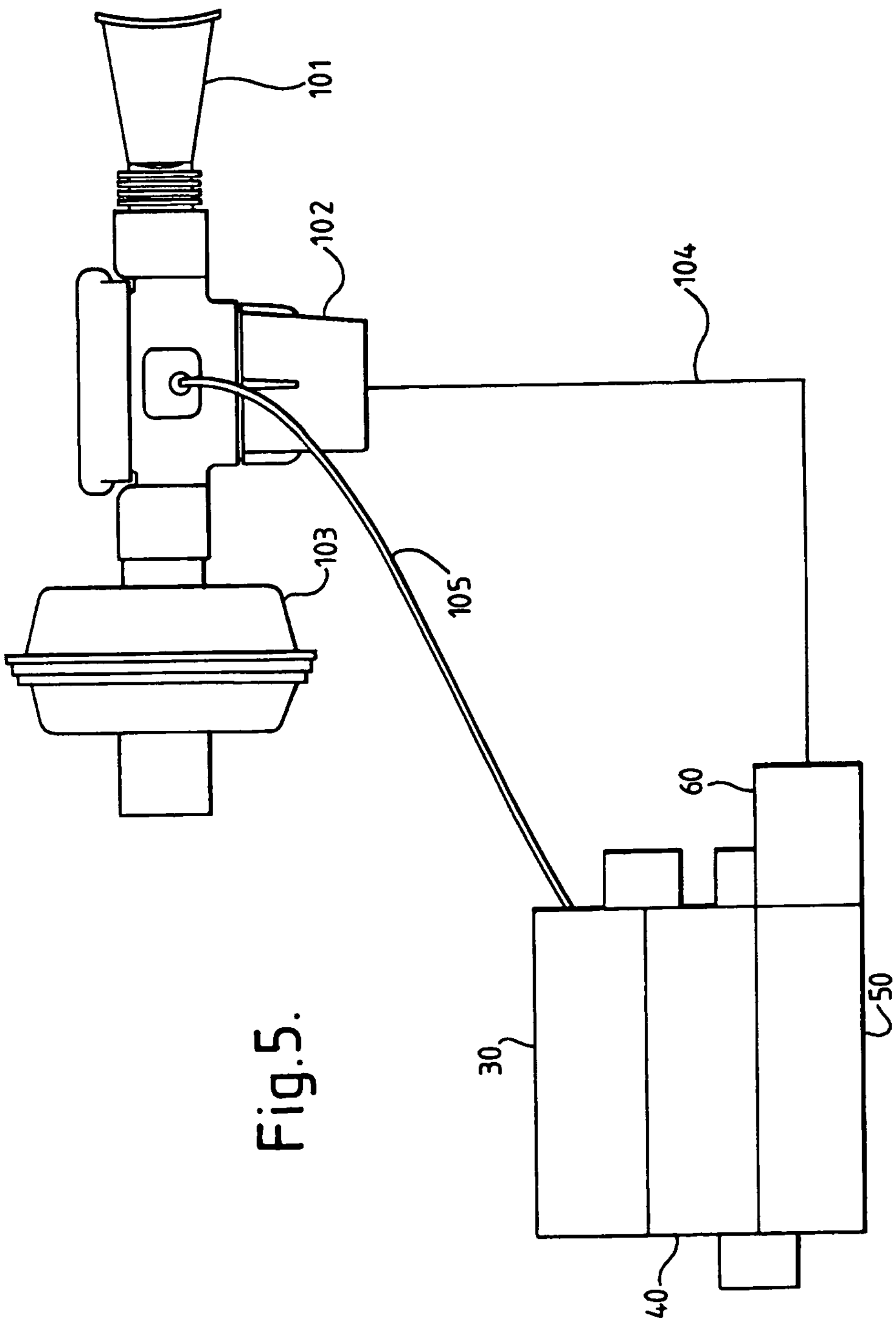

Fig.5.

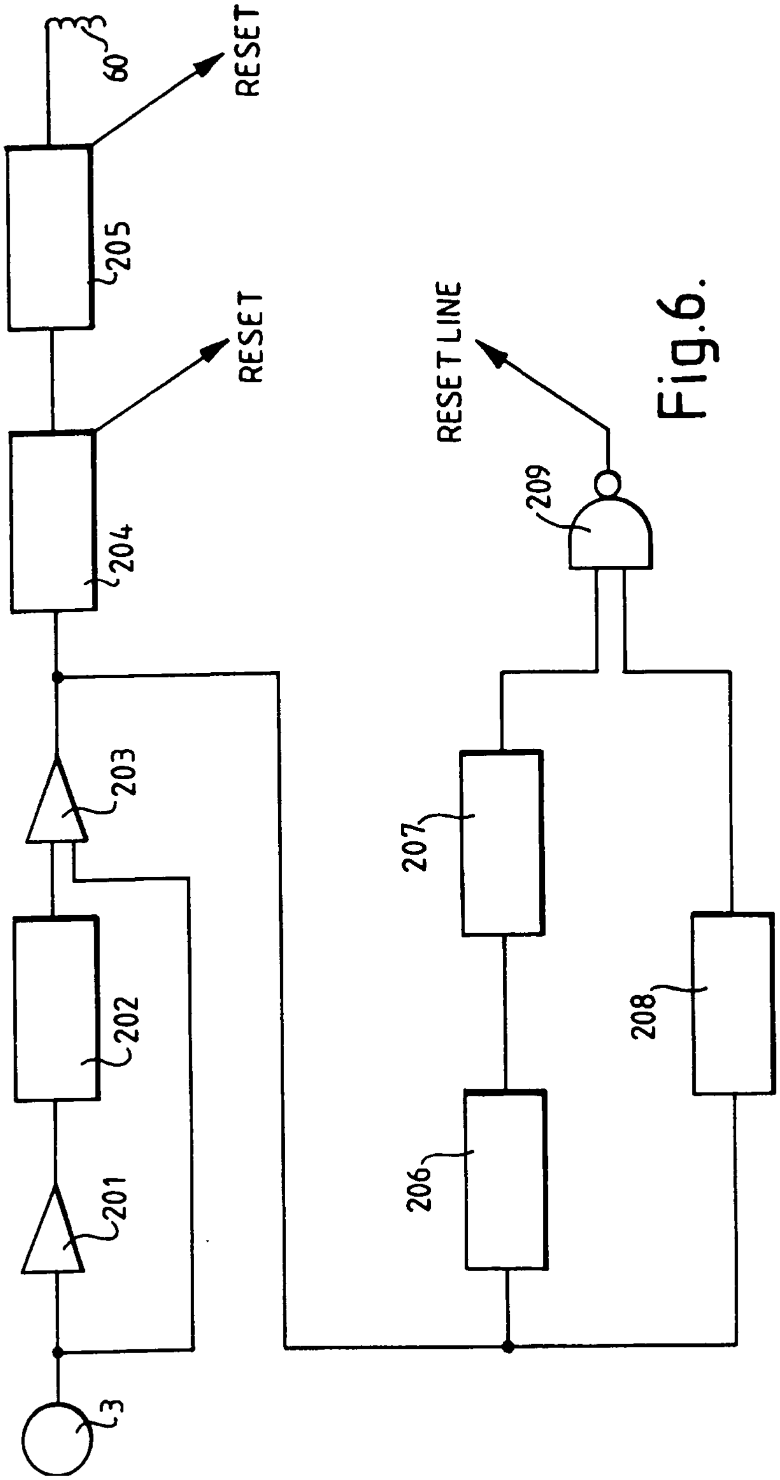

Fig.6.

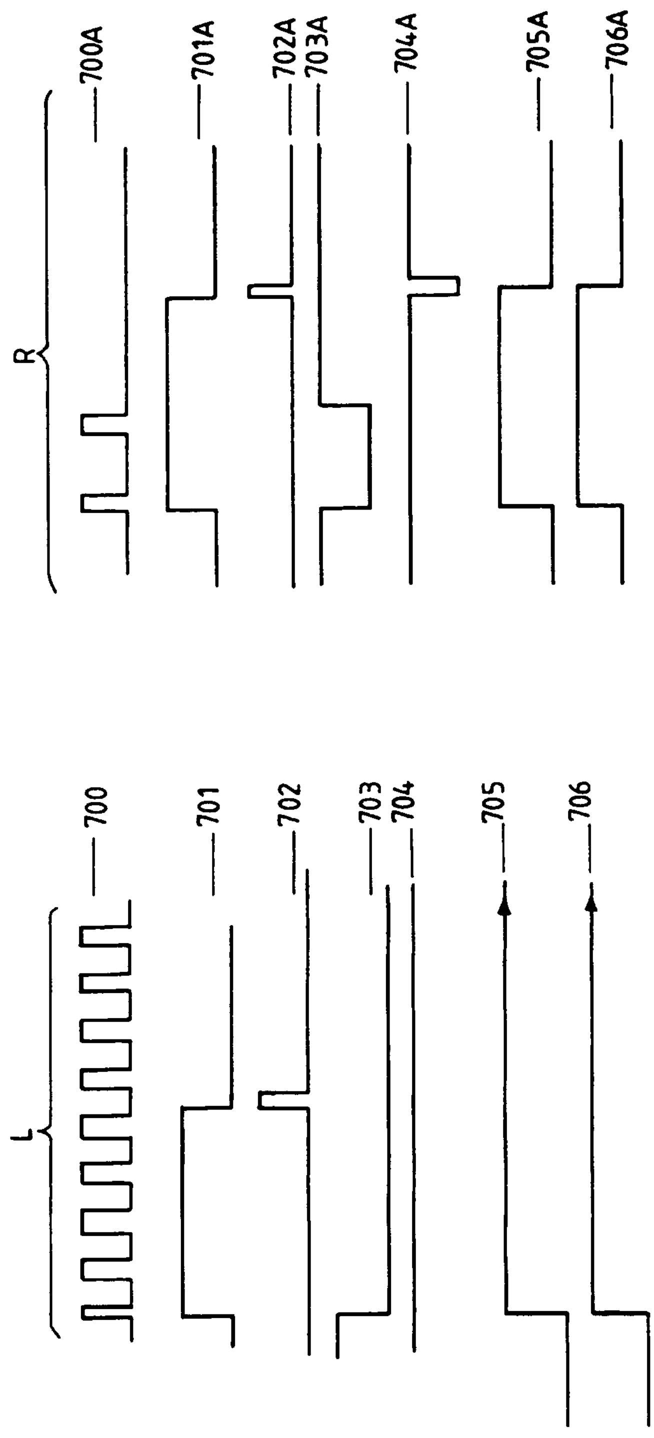
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Fig.7.

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EUROPEAN SEARCH REPORT

Application Number
EP 93 30 6974

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
X	WO-A-89 06147 (ETELÄHÄMEEN KEUHKOVAMMAYHDISTYS R. Y.) * page 7, line 15 - line 29 * * figures 2A,3 *	1,10	A61M15/00
X	DE-A-28 09 255 (ROSENTHAL) * page 10, line 3 - page 12, line 23 * * figure 1 *	1	
Y	EP-A-0 461 281 (ATOCHEM NORTH AMERICA, INC) * column 3, line 6 - column 7, line 39 * * figures 1-3 *	1,3-7	
Y	EP-A-0 387 222 (AKTIEBOLAGET DRACO) * column 2, line 13 - line 27 * * column 4, line 51 - column 5, line 23 * * column 6, line 9 - line 50 * * column 7, line 6 - line 27 * * figure 7 *	1,3-7	TECHNICAL FIELDS SEARCHED (Int.Cl.5)
A	EP-A-0 178 925 (UINVERSITY OF AUCKLAND) * page 5, line 32 - page 7, line 28 * * figure 3 *	2	A61M
A	US-A-5 000 173 (ZALKIN ET AL.) * column 1, line 64 - column 2, line 29 * * figure 1 *	8	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	30 November 1993	Schönleben, J

CATEGORY OF CITED DOCUMENTS

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